Library

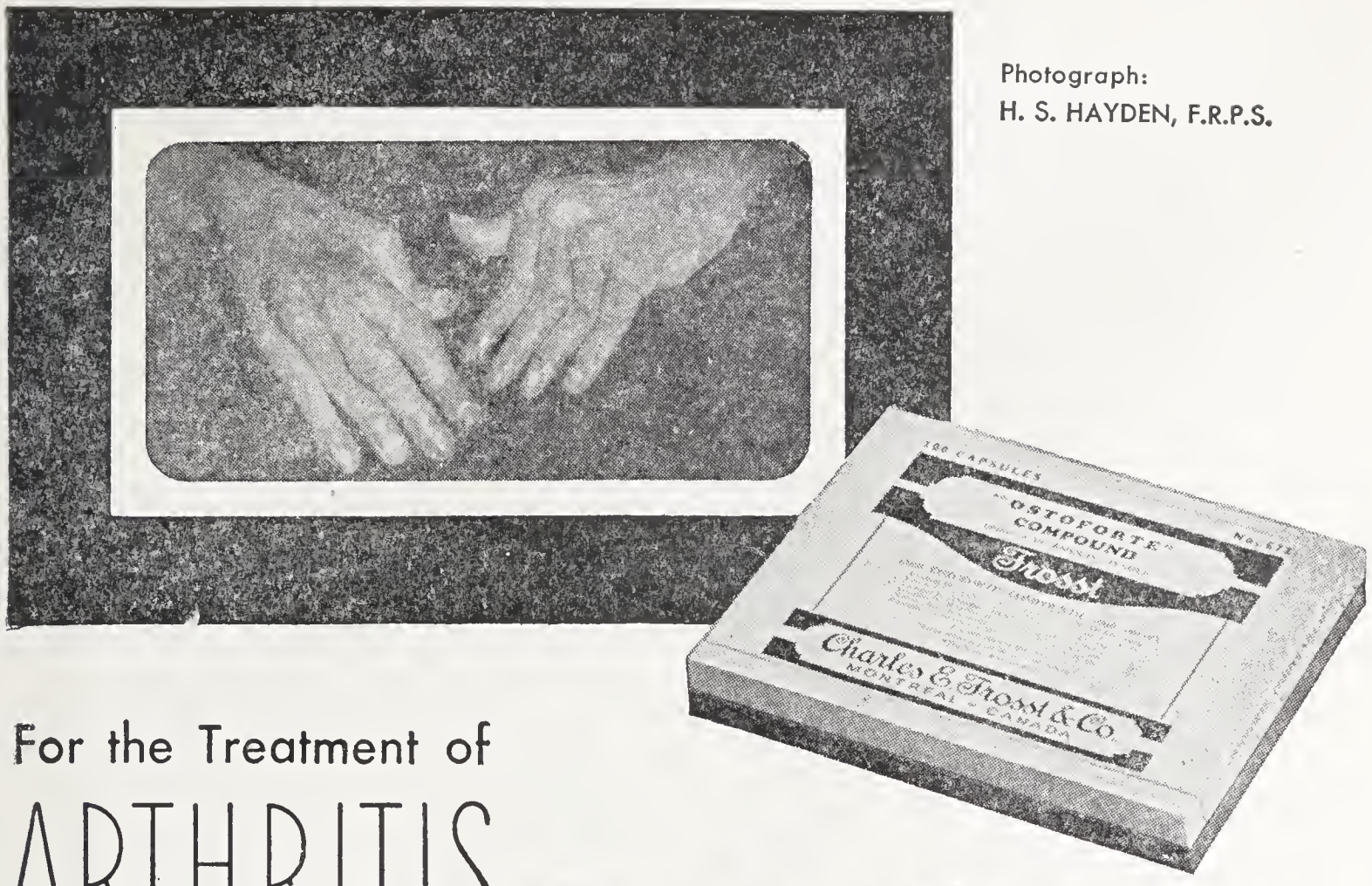
of the

University of Toronto

P78-0727 (27)

Digitized by the Internet Archive
in 2018 with funding from
University of Toronto

https://archive.org/details/medjournalOct1947uoft



Photograph:
H. S. HAYDEN, F.R.P.S.

For the Treatment of

ARTHRITIS "Ostoforte" Compound

(S. E. C. No. 671 "Frosst")

For those cases where the normal diet is adequate in Vitamin B factors and Vitamin A.

"OSTOFORTE"

(S. E. C. No. 651 "Frosst")

Each capsule contains 50,000 Int. Units of Vitamin D.

IMPORTANT: *Ostoforte Compound and Ostoforte should not be administered to patients with "impaired kidney function", nor to children in repeated doses.*

Many patients suffering with arthritis are of necessity confined indoors. They are often physically inactive and their appetites may be diminished, or their diet may be restricted for therapeutic reasons. Ostoforte Compound Capsules, in addition to supplying massive doses of Vitamin D, found effective in many arthritics, will supply adequate amounts of the other essential vitamins, thus making up for deficiencies in their diet in these respects.

FORMULA:

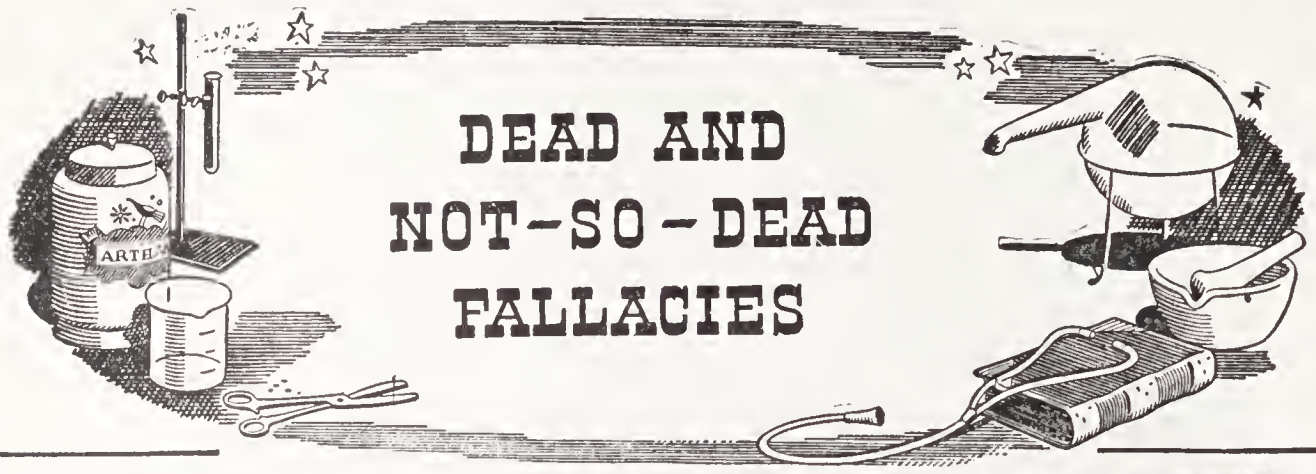
	In each Capsule	*In Average Daily Dose (4 capsules)*
Vitamin D - - -	50,000 Int. Units	200,000 Int. Units
Vitamin A - - -	1,666 Int. Units	6,664 Int. Units
Vitamin B_1 (Thiamine HC1)	0.67 mg.	2.67 mg.
Riboflavin (Vitamin B_2)	1.00 mg.	4.00 mg.
Niacinamide - - -	6.67 mg.	26.67 mg.
Vitamin C (Ascorbic acid)	15.00 mg.	60.00 mg.

MODES OF ISSUE: Boxes of 50 and 100 capsules for your prescription.

DOSE: Up to six capsules daily. Complete dosage table on request.

Frosst SINCE 1899 THE SYMBOL OF PROGRESS IN PHARMACEUTICAL RESEARCH

Charles E. Frosst & Co.
MONTREAL CANADA



DEAD AND NOT-SO-DEAD FALLACIES

In ancient Greece, the roots of the mandrake were regarded as a panacea.

To prevent townspeople from picking them, however, the men who made their living selling the root said the mandrake shrieked when uprooted—*and that anyone who heard the weird sound fell dead!*

Some folks believe that unless canned foods are thoroughly cooked they should not be served.

In the canning process foods are thoroughly cooked. All you need do is heat and season to taste.

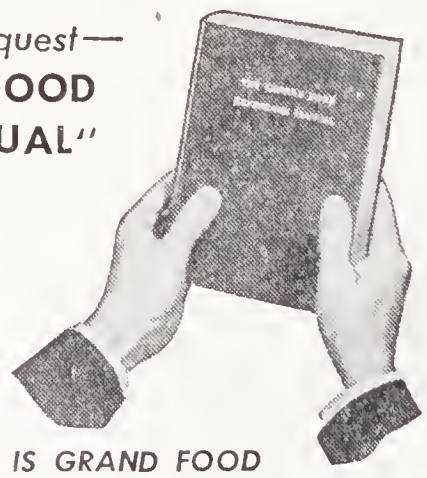
CANCO **AMERICAN CAN COMPANY**

KENTVILLE MONTREAL HAMILTON TORONTO WINNIPEG VANCOUVER

Now available on request—

"THE CANNED FOOD REFERENCE MANUAL"

—a handy source of valuable dietary information. Please fill in and mail the attached coupon now.



CANNED FOOD IS GRAND FOOD

AMERICAN CAN COMPANY
92 King Street East, Hamilton, Ont.

Please send me the new Canadian edition of "THE CANNED FOOD REFERENCE MANUAL," which is free.

Name.....

Professional Title.....

Address.....

City.....Province.....

Volume XXV Toronto, October, 1947 Number 1

The University of Toronto Medical Journal

(AN UNDERGRADUATE PUBLICATION)

This journal is published six times a year, November to April, by the Medical Society of the University of Toronto, to serve as a medium for student expression and to bring to the student recent articles of scientific interest.

$1.50 per volume. 25c. per single copy.

ADVISORY STAFF
PROF. A. E. LINELL, M.D., Ch.B.(Manc)
J. H. COUCH, M.A., M.B., F.R.C.S.(Edin.), F.R.C.S.(C.)
J. HEPBURN, M.B., F.R.C.P.(C.)
D. Y. SOLANDT, M.A., M.D., Ph.D.(Lond.)
A. M. WYNNE, M.A. Qu., Ph.D.
H. H. HYLAND, M.D., M.R.C.P.(Lond.), F.R.C.P.(C)

Editor-in-Chief
E. A. McCULLOCH

Associate Editor
R. H. SHEPPARD

Assistant Editor
M. L. BUNKER

Managing Editor
F. L. CLEMENT

Features Editor
R. K. GRAHAM

Abstracts Editor
E. R. YENDT

Circulation Manager
D. J. McCULLOCH

Contributing Editors
2nd Year (Premedical)—S. WAX
1st Year (Medical)—B. E. PIVNICK
2nd (Medical)—M. J. T. SEDLMEIR
3rd (Medical)—EDWARD FISH
4th (Medical)—R. W. RUTHERFORD

Address all communications to Room 107, Anatomy Building

EDITORIAL

This is a time of changes. Four heads of Departments have resigned. These are famous men, and nothing that we can write will add to their fame. Gallie is a name which surgical students will be learning a hundred years from now. Dr. Graham is a trail-blazer in medical teaching. Dr. Hunter has added basic ideas to our knowledge of nutrition, although he will be best remembered by medical students for his crystal-clear lectures. Dr. Farrar has helped to make psychiatry one of the first arms of medical help.

The new appointments are welcomed by us all. Only one of those announced is a stranger to us. Dr. A. B. Stokes, the new professor of psychiatry, is from London, England. We hope that he will like Canada, and this University. Dr. Farquharson, Dr. Janes, and Dr. Dauphinee go their new posts assured of our appreciation.

* * * * *

We are full of hope that this JOURNAL will be published on or near the date that it bears on its cover. In this way, we will have finally caught up with the accelerated course. It is the first ambition of this staff to bring out the JOURNAL on time, and containing articles of real interest and high quality. This is only possible with the co-operation of the students. We hope that everyone who has an idea, will write an article. We would also like to thank the doctors who have so generously contributed in the past, and to ask them to continue to give us their support with our assurance that their articles are read and studied, and thought about by the students.

DEHYDRATION

D. LAURENCE WILSON, M.D.

The problem of dehydration is of peculiar interest, not only because of its obvious practical importance, but because it serves to illustrate the application of so many of the present concepts of the field of water and electrolyte balance. And it is necessary to begin with a brief discussion of one of these concepts which has made necessary a reorientation toward the meaning of dehydration. One refers now to the differentiation of body fluids into anatomically and physiologically distinct phases or compartments. Not so many years ago, investigation of these problems was impeded by the difficulty of interpreting results of tissue analyses. Now a fragment of tissue contains not only its cells with their water and solid content, but also a quantity of the interstitial fluid which fills the interstices between them, and which has quite a different chemical composition. As long as analytical results had to be expressed in terms of whole tissue, attempts to evaluate the distribution of water and electrolytes and their movements into and out of the cells were inevitably crude approximations. It has been the development of techniques permitting the differentiation of these two phases of tissue water, and specifically the elaboration of the "chloride space" concept, which have given impetus to progress in this field of physiology. The use of the chloride space in calculating the proportion of extracellular to intracellular fluid, involves the assumption that no chloride is present within the cells. It is then possible to calculate the volume of extracellular water in, say, a sample of muscle, from the chloride content of the sample and the concentration of chloride in the extracellular fluids of the organism under study—two values open to experimental determination. The assumption that all chloride is extracellular is valid only for certain tissues, notably muscle and liver; it is supported by the close correlation between the magnitude of the extracellular space so calculated and that estimated by histological methods (43).

Modern techniques permit us to distinguish three main compartments of body water—plasma, interstitial fluid and intracellular fluid—each with its characteristic chemical anatomy. During disturbances of normal water and electrolyte distribution, we must bear in mind that these compartments, while interdependent, may not be affected to the same extent or even in the same direction. And it will not, then, be surprising to meet dehydration confined to the extracellular fluid, or to the intracellular fluid; or that shifts of water may take place from one phase to the other without any alteration in total body water.

Normal Distribution of Water and Electrolytes. In approaching our subject, it would be well to begin by crystallizing in our minds the essentials of the structures of these compartments, and of the ways in which water normally enters and leaves the body.

Water ordinarily comprises about 70% of the body weight. This may be broken down into intracellular water (50% of body weight), interstitial water (15%), and plasma water (5%). Thus well over half of the total amount lies within the cells. It is present of course, in the form of dilute solutions of electro-

lytes and protein. And while the interstitial fluid closely resembles an ultrafiltrate of plasma, the electrolyte composition of these two fluids presents striking qualitative differences from that of the intracellular solution. These differences vary considerably from tissue to tissue, but it may be stated that, in general, extracellular fluid is characterized by sodium, calcium and chloride; intracellular fluid, by potassium, magnesium and phosphorus. Since we shall be concerned largely with sodium, potassium and chloride concentrations, these values for a number of fluids are compared in Table 1.

TABLE I.

Compositions of Extracellular and Intracellular Fluids*

	Cl	Na	K
	mM/l.	mM/l.	mM/l.
Extracellular fluid:			
Serum ultrafiltrate	111	145	3.3
	mM/kg. water	mM/kg. water	mM/kg. water
Intracellular fluid:			
Skeletal muscle	3	7	155
Cardiac muscle	7	15	142
Liver	12	5	145
Brain	3	27	184

*All values quoted from Darrow (8). This author has found evidence from his data to suggest the above small intracellular chloride values, and makes allowance for them in calculating the chloride space.

The turnover of water by the body occurs at a rate of between two and three liters per 24 hours. Assuming a turnover of 2,500 ml., we may say that the greater part enters the body in the form of ingested liquid or moist food, while the remainder—perhaps 300 - 500 ml.—represents water of oxidation, derived from the metabolic breakdown of organic food constituents. The debit side of our balance sheet is summarized in the following table (3).

	ml./24 hours
Skin (average temperature and humidity)	500
Expired air	350
Urine	1,500
Feces	150
Total	2,500

Although only 150 ml. of water is lost daily in normal feces, the gastrointestinal secretions may figure very prominently indeed in the water balance of disease. Let us examine the accompanying table of the 24-hour volumes of such secretions as quoted from Rowntree by Gamble (16).

Saliva	1,500 cc.
Gastric Juice	2,500 cc.
Bile	500 cc.
Pancreatic Juice	700 cc.
Succus entericus	3,000 cc.
Total	8,200 cc.

We see that something over eight liters of fluid is poured daily into the adult human gastro-intestinal tract—a quantity which becomes significant when we reflect that it is about twice the volume of the blood plasma. Ordinarily this fluid is almost entirely reabsorbed in the colon, so that we may visualize a sort of circulation of water and electrolyte from the plasma, through the stomach and intestine, and back into the plasma again. If this circulation is upset by vomiting or diarrhoea, or both, relatively enormous quantities of water and electrolyte may be lost from the body in a short time.

The balance between intake and output is normally regulated between narrow limits by the kidney. Since water is such an important constituent of cells, it is to be expected that the balance will be positive during growth—about 3g. of water is laid down per gram of protein (3). In starvation or wasting diseases, on the other hand, similar amounts of water are lost.

Causes of Dehydration. What, in general, are the causes of dehydration? First of all, of course, there is the relatively uncomplicated deficit of body water following simple water deprivation. "Relatively" uncomplicated, because, as we shall see, the kidney ordinarily maintains the osmotic value of body fluids under these circumstances by excreting additional electrolyte. To the extent to which this adjustment succeeds, there will be a net loss of body electrolyte which must be replaced bef re recovery is complete; to the extent to which it fails, there will be an increase in the osmotic value of the body fluids.

General or local dehydration is often produced in a more roundabout fashion. Since the behaviour of body water is inextricably linked with that of its dissolved electrolytes, any variation in total electrolyte leads inevitably to variation in body water. And, what may seem at first remarkable, whether the absolute amount electrolyte increases or decreases, the result will be some form of dehydration.

Let us take first the case of an increase in body base. The most obvious example is an excessive salt intake which can produce a primary elevation of electrolyte concentration. As we shall see, the normal kidney responds to this state of affairs by increasing the quantity of base excreted. This can be accomplished in part by the excretion of a more concentrated urine; but when this compensatory mechanism has been pushed to its physiological limit, the kidney can deal with the additional base only by increasing the volume of urine at the expense of body water. Whether or not the renal effort succeeds in restoring the electrolyte pattern to normal, there will result a net loss of body water. In other words, we find an exaggerated form of the changes noted in simple water deprivation.

A less obvious cause of dehydration is a primary *reduction* of body base unassociated, at least initially, with water loss from the body as a whole. The examination of this type of change has taught us a good deal both in our understanding of the fundamental interrelationships of water and electrolyte, and in the treatment of human disease. It appears to have been clearly differentiated for the first time by the German worker, Kerpel-Fronius (27), who produced extracellular base depletion in rabbits by a procedure suggested by the earlier work of an American group under Darrow at Yale (39). When a volume of 5% glucose solution is injected intraperitoneally into animals, it rapidly comes into equilibrium with the diffusible elements of the plasma. Hence, when the procedure is completed several hours later by drawing off from the peritoneal cavity a volume of fluid equal to that injected, the net effect is the removal of the diffusible electrolyte dissolved in the same volume of serum, without any removal of water. While this technique permits the controlled depletion of experimental animals, it must not be supposed that the condition is a laboratory curiosity. Actually, any situation in which loss of water plus electrolyte occurs, such as diarrhoea or excessive sweating, may be transformed by the ingestion of water without salt, into a pure state of base depletion. Now the loss of extracellular electrolyte leads to a lowering of the osmotic pressure of the plasma and interstitial fluid. As we shall see in some detail later on, the characteristic reaction of the body to this state of affairs, is the removal of water from the extracellular to the intracellular compartment, producing, in effect, an extracellular dehydration. Indeed, these animals *appear* dehydrated, showing oliguria, dryness of mucous membranes, and loss of the normal turgor of their skin and subcutaneous tissues; yet there may have been little or no reduction in total body water.

We have seen then, that there are two basically different ways in which dehydration may be produced: first, simple water deficit with which we may group the closely similar syndrome which follows excessive salt intake; and second, primary base deficit, in which the *total* body water might remain unchanged. However, we must not take this arbitrary division too seriously. Actually, because of the behaviour of the kidneys, either of the pure types tends to be converted, sooner or later, into a mixed type in which water *and* base depletion coexist. And, in clinical practice, where dehydration ordinarily follows abnormal loss of sweat or urine or gastrointestinal secretions, this mixed character is likely to obtain from the beginning. Thus, excessive sweating leads to the dehydration of heat exhaustion which is associated with the loss of considerable quantities of sodium chloride, contained in sweat to the extent of 10-90 mE/liter. Of course, if, as often happens, the victim is simultaneously ingesting generous quantities of water, the actual water loss may be compensated, and a pure state of base depletion produced. Again, in severe diarrhoeas, and in the vomiting of intestinal obstruction, the gastrointestinal secretions, which would ordinarily have been reabsorbed in the lower bowel, are lost to the body with their important complement of dissolved electrolyte. When we come to the kidney, we find that prolonged diuresis may cause depletion of both water and salt, although here again, if water intake is adequate, salt loss may predomi-

nate. Such a state of affairs occurs, for example, in the diuresis of diabetes mellitus. In this connection, we may pause to note that glucose does not tend to displace sodium and chloride from the urine, but rather has been shown by a number of investigators to actually accelerate their excretion. Thus, as Peters has pointed out, glycosuria is peculiarly dehydrating (37). Again, dehydration may result from the polyuria of chronic renal disease—particularly if the intake of salt has been limited as a therapeutic measure. This may be particularly serious in the so-called "salt-losing" nephritis in which the base-saving ammonia mechanism is seriously impaired, so that inordinately large amounts of sodium are excreted from the body (17).

Extracellular—Intracellular Relationships. Our next task will be to look more closely at the internal changes which occur within and between the various fluid compartments as a result of dehydration. By referring repeatedly to "extracellular fluid," I have intentionally given the impression that changes in the interstitial fluid essentially parallel those in the plasma. This view would appear to follow logically from acceptance of the Starling theory of the formation of interstitial fluid as an ultrafiltrate of plasma. And, from a factual point of view, it is now, I think, adequately documented by experiment (23, 32). Let us proceed to relate changes in this extracellular compartment to those within the cells. For our purposes, we can look upon the intracellular and extracellular compartments as two solutions separated by a semi-permeable membrane. They differ, as we saw earlier, in that the solution outside the cells is characterized by sodium and chloride, that inside the cells, by potassium and phosphorus. The two phases are in apparent osmotic equilibrium across the cell membrane, and this equilibrium must necessarily be upset whenever the osmotic value of the extracellular space is disturbed by the processes of dehydration. One might think of three possible ways in which equilibrium could be restored after such a disturbance. Thus, adjustment could be effected by shifts of water across the membrane, by similar shifts of solutes, or by changes in the osmotic activities of some substance or substances, most likely within the cells. All three mechanisms probably occur.

Let us consider first the possibility of shifts of water between the phases. There appears to be little doubt that it is mainly in this way that osmotic adjustments come about. The earliest evidence was presented in 1935 by Darrow and Yannet of Yale, who carried out experiments on two groups of dogs, rabbits and monkeys (9). In the first group, they induced loss of extracellular electrolyte by the Kerpel-Fronius procedure; in the second, increase in extracellular electrolyte with little change in body water by means of similar injections of hypertonic sodium chloride. In short, they lowered extracellular osmotic pressure in one group, raised it in the other. By following the haematocrit and the concentrations of various plasma constituents, they were able to obtain convincing evidence that appropriate shifts of water in or out of the cells occurred in response to changes in the extracellular osmotic pressure. In a later publication, these same investigators reported a much more extensive experiment on the effect of extracellular electrolyte in cats, in which their earlier conclusions

were corroborated by actual tissue analyses (48). In the cases of liver and skeletal muscle, they were able to demonstrate clearly that the volume of intracellular water varies inversely with the concentration of sodium outside the cells; in cardiac muscle, on the other hand, no such relationship appeared to exist. Their findings in skeletal muscle are confirmed by the experiments of Mellors *et al.* on the dog (31).

I want next to consider the possibility of shifts of electrolyte across the membrane. And here the situation is much less clear. From the separation of sodium and potassium in the body, we might expect to find these ions unable to pass the cell membrane. On the contrary, while their movements probably do not make a great contribution to osmotic adjustments of most tissues, they almost certainly occur, at least in the case of sodium. Thus, it was found by Yannet and Darrow (48) in the cat, that the small intracellular sodium fractions of skeletal and cardiac muscle vary directly with the extracellular sodium concentration, findings confirmed in the skeletal muscle of the dog by Mellors and his group (31). In liver, on the other hand, Yannet and Darrow found no such correlation. There is also evidence that an increase of extracellular base above the normal level is followed by a rise in the intracellular sodium fraction of the skeletal muscle of the rabbit, rat, and cat (46, 29, 26). Of course, in the light of the small amounts of sodium present within most cells, it must be realized that these changes can be of only limited help in restoring osmotic equilibrium.

It would be much more significant if the large quantity of intracellular potassium were free to cross the membrane to correct osmotic inequalities. However, the available evidence seems to preclude the utilization of this mechanism in any but a minor role. Because it is not a particularly significant aspect of our topic, and because it is confused by a mass of contradictory observations which we cannot hope to unravel in the space available, I propose only to sketch in a very rough outline of the more pertinent facts. First of all, direct analyses disclose no significant changes in the potassium concentration of either compartment in any form of dehydration. On the other hand, balance experiments by a number of observers (4, 12, 13, 14, 25, 27) have demonstrated a negative potassium balance in both types of dehydration. This apparently represents a loss of intracellular potassium; but since potassium does not accumulate in the extracellular fluids even after ligation of the ureters (44), the loss seems contingent on the presence of sufficient renal activity to remove it promptly from the body. The factors which operate to produce these changes are completely obscure. However, we might note in passing that were it possible for this potassium to accumulate in the extracellular fluids during severe dehydration, the condition would become much more dangerous than in fact it is. Associated with the negative potassium balance is a negative nitrogen balance, which may be interpreted as evidence for increased tissue catabolism in dehydration. And it is by no means clear that the loss of potassium may not be accounted for by the destruction of protoplasm, although I believe that the burden of evidence does support an independent potassium loss. However that may be, the net effect of the two processes, loss of intracellular potassium and tissue breakdown, make available a quantity of intracellular water to share the burden of dehydration.

We mentioned a third possible mechanism for adjustments between the two phases—a change in osmotic activity of some body substance. On this topic we have only indirect evidence to guide us. In their earlier experiments on base-depleted dogs, Darrow and Yannet (10) observed that the ratio of the concentrations of extracellular sodium and intracellular potassium underwent rather wide fluctuations. Later, the same authors (48) found that the shifts of water into the cells of cats depleted of extracellular electrolyte was, in the case of skeletal muscle only 1/3, and in liver, only 1/2 of that predicted from the initial disparity in electrolyte concentration—although in cardiac muscle, they could not detect this phenomenon. Similar findings were reported for dog skeletal muscle by Mellors *et al.* (31). Darrow and Yannet interpret their data as suggesting that the osmotic activity of the intracellular constituents of skeletal muscle and liver is variable and constitutes a third device by which osmotic equality with the extracellular phase may be maintained.

Let us try to summarize this variety of observations. Using muscle tissue as our standard, we may say in general that variations in the osmotic pressure of serum found in either type of dehydration are adjusted mainly by appropriate shifts of water between the extracellular and intracellular compartments. The small intracellular sodium fraction appears to be diffusible and to vary with the extracellular base concentration, thereby aiding to offset osmotic inequalities. While the intracellular potassium seems never to contribute directly to extracellular base, it does, in the presence of facilities for its immediate excretion, leave the cells and thus make its complement of intracellular water available to the interstitial fluid; in this it is assisted by the associated protein breakdown. Finally, as we have seen, certain observations suggest that these mechanisms do not satisfactorily account for osmotic adjustments in experimental dehydration, and that a change in osmotic activity of some intracellular constituent may be an additional factor.

Although this is true of skeletal muscle, certain differences in the cases of cardiac muscle and liver have been pointed out. Moreover, in the brain, it appears from the work of Yannet (47) that the movement of water between the two phases does not occur to a significant extent, equilibrium being maintained instead by shifts of potassium across the cell membrane. Thus it must be emphasized that no general pattern can be laid down, and that the response of each tissue must be separately evaluated.

General Responses to Dehydration. It remains for us to discuss the reactions to dehydration of the several mechanisms regulating the water balance of the body as a whole. Regulation of water intake is of prime importance, and, of course, any consideration of this factor must centre about the problem of thirst. The latter has long been a source of controversy between those who hold that thirst is a generalized craving of the body, and those who feel that it is merely a local oral and pharyngeal sensation, secondary to decreased salivary secretion. From an historical point of view, it appears that Claude Bernard, as usual, had the first word. He observed the drinking habits of a horse with an oesophageal fistula and a dog with a gastric fistula, in which water was eliminated from the

body before it could be absorbed (2). Both animals showed unquenchable thirst and would drink until exhausted, rest a while, and then return to drink again. Bernard reasoned that a few swallows should be as effective in moistening the oral and pharyngeal mucosa as the enormous quantities actually ingested at a time; he therefore suggested that thirst was somehow a general sensation. Of the opposing theory, that thirst is of local origin, Cannon has been the leading exponent. And since the latter idea was much more concrete and accessible to experiment than the first, it long enjoyed the ascendancy. Of the well-known evidence put forward in support of the importance of reduced salivary secretion in thirst, we shall say little here since they have been summarized elsewhere (3, 11). In general, the findings that thirst can be induced by atropine and allayed by pilocarpine or by cocainization of the oral mucosa, point convincingly to the importance of this mechanism. That it is not the whole story, however, is equally apparent. Montgomery has shown that dogs experimentally deprived of salivary secretion do not increase their water intake (33), a finding confirmed by Gregersen and Cannon (22). Similar observations have been reported in a human with congenital absence of the salivary glands (1). It has remained for more recent work to clarify the nature of the "general" stimulus inducing thirst. Two papers have been of critical importance. In the first, Gilman (21) injected dogs first with hypertonic sodium chloride, and later after a rest period, with an equal volume of isosmolar hypertonic urea. The osmotic pressure and specific gravity of the serum were determined before and after each injection, and a record of water intake was kept. In both experiments, he found, as might be expected, approximately the same rise in serum osmotic pressure. In the sodium chloride experiment, the specific gravity fell markedly after injection, whereas it remained unchanged after the injection of urea. Here the explanation is obvious. Since urea readily penetrates cells it diffuses through both compartments without producing disturbances in water and electrolyte equilibrium; sodium chloride, on the other hand, is mainly confined to the extracellular compartment, and the shift of water out of the cells which restores osmotic equilibrium, also dilutes the plasma proteins and lowers serum specific gravity. The significant finding in this experiment was the difference in water intake in the two groups. The average voluntary water consumption by the animals after sodium chloride injection was double their consumption after urea injection. Since the two solutions led to identical *osmotic* changes in both intracellular and extracellular compartments, the most obvious variable with which we can relate the intensity of thirst seems to be an absolute loss of intracellular water. This view is strengthened by the observation that animals depleted of extracellular base do not show thirst, although they present the other signs of dehydration and may have lost water from the body as a whole. Such animals, of course, have an *increased* intracellular water content. This phenomenon was noted originally by Darrow and Yannet (9) and by Gilman (20) in the course of experiments for other purposes. It remained for Nadal and his co-workers to investigate it in some detail in a most interesting experiment on humans (35). Their subjects underwent dehydration by both simple water deprivation and base

depletion. The latter condition was induced by withdrawal of gastro-intestinal secretions through a duodenal tube while a free water intake was permitted. And following this procedure, there was marked haemoconcentration, but no thirst, even though water was withheld. In contrast, severe thirst occurred early after water deprivation, although haemoconcentration was much less marked than that which followed base depletion. One cannot, then, escape the conclusion that the sensation of thirst represents, at least in part, a response of the body as a whole, for which the adequate stimulus is probably a loss of intracellular water.

We might note in passing that instinctive cravings of this type appear to play a part in regulating the intake of substances other than water. The tendency of children, allowed a free choice of diet, to regulate with uncanny accuracy their intake of essential metabolites such as protein, calcium and vitamin D, has been the subject of interesting comment by the pediatrician Sweet (42). In recent years, the remarkable work of Richter (38), has demonstrated similar phenomena in the rat. For example, he has shown that these animals will correct such conditions as acidosis and salt deficiency by choosing to drink dilute sodium lactate or sodium chloride left in the cage as an alternative to water. Thus, it may well be that we should regard thirst only as a special example of a very general group of psychobiological mechanisms, many of which may be obscured, in the human, by social custom.

Having considered the regulation of intake, we come now to that of output of water and electrolyte in dehydration. As we saw earlier, this occurs mainly through insensible water loss (augmented in warm surroundings and in disease by sweating) and through the kidneys. Insensible water loss, sometimes amounting to a liter or more daily, occurs through the lungs and the skin. As long as sweating is avoided, this may be regarded as a loss of distilled water (15). Sweat, on the other hand, contains sodium chloride in amounts ranging from 10 to 90 milli-equivalents per liter (11) and thus represents a hypotonic salt solution. It is interesting that women differ from men in that they can delay the onset of sweating at moderately high temperatures by reducing heat production, and that they tend moreover to secrete a fluid containing less sodium chloride. Now there is no doubt that some control can be exercised over these losses in dehydration. Thus Peters in a recent review (37) notes that insensible water loss tends to vary with the water load in the body. Moreover, Dill (11) has shown that after moving to a hot climate, humans rapidly reduce the electrolyte loss in sweat by secreting a more dilute solution.

Nevertheless, it must be remembered that these water losses subserve an important role in regulating body temperature, and cannot be markedly reduced without grave consequence to the organism. It is partly for this reason that regulation of renal loss of water and salt represents a much more important means of adjustment in dehydration. Of course the kidney has other equally important duties. It must also regulate the electrolyte content of the plasma, guarding its osmotic value, its reaction, and the levels of such important inorganic materials as calcium and potassium which may be allowed to vary only

within narrow limits without harm to the body. Moreover, it must see to the excretion of a number of the end-products of metabolism, especially nitrogen metabolism, such as urea, creatinine and uric acid. These functions are obviously interrelated, and, indeed, we cannot intelligently discuss any one of them without bringing in the others. The adequate stimuli for the specific alterations in renal function, which enable the kidney to maintain the internal environment in so many dimensions simultaneously, are largely obscure. Nevertheless, we can profitably dwell for a moment on the patterns of renal activity as they apply to the various states of water depletion.

One generalization we may draw from the experimental evidence is that the kidneys appear much more sensitive to osmotic than to volume changes in the plasma. Thus, the administration of equal volumes of different solutions may evoke quite dissimilar reactions on the part of the kidney, although all have had an identical effect on the *volume* of body fluid. Pure water is rapidly excreted—taking with it small amounts of extracellular electrolyte (41)—while an equal volume of isotonic sodium chloride solution is only gradually eliminated (40). Isotonic potassium chloride, on the other hand, is excreted at least as rapidly as pure water (5). Hence it would appear that the relative retention of the sodium chloride was due partly to its isotonicity, partly to its qualitative similarity to the electrolyte pattern of plasma. Nevertheless, because this solution is eventually excreted, it is evident that the kidney also responds, though more slowly, to changes in the volume of body fluids. From this general tendency of renal activity to guard plasma composition before plasma volume, emphasized by Gamble (16), the close interdependence of body electrolyte and body water is readily understood. Thus, where the concentrations of electrolytes are not already disturbed, the excretion of extracellular water tends to be accompanied by its complement of sodium and chloride; while intracellular water is ordinarily excreted only along with equivalent amounts of nitrogen, phosphorus, and potassium (19). Conversely, it is of the greatest practical importance that the biochemical lesion in dehydration associated with base depletion cannot be repaired by the ingestion of water alone. Hartwell and Hoguet observed in 1912 (24) that dogs with pyloric obstruction could be kept alive for several weeks with parenteral injections of sodium chloride solution. Isotonic glucose has no such effect (18). Similarly, in the base-depletion experiments of Nadal *et al.* (35), haemoconcentration and symptoms of dehydration persisted in spite of an adequate water intake. In other words, water cannot ordinarily be retained in the body without its complement of base.

This tendency of kidney function is found in dehydration. If, for any reason, water is lost in excess of electrolyte, the kidneys will, providing their function is not too severely impaired, tend to reduce extracellular osmotic pressure by excreting additional sodium (25, 37). On the other hand, when body base is depleted in excess of body water, the kidneys may attempt to excrete an equivalent amount of water by reducing sodium excretion in the urine (10, 25, 27, 35). Thus, through the mediation of renal function, either primary type of dehydration is likely to be converted into a mixed type with a deficit of both

water and base. Since McCance and Young (30) have shown in the human that neither renal blood flow nor glomerular filtration (as evidenced by diodone and inulin clearances) are reduced in dehydration, these adjustments seem to be effected by modification of tubular reabsorption. However, if the degree of dehydration is severe, a certain amount of water may be retained without its equivalent of sodium chloride, i.e., in such an emergency, the kidney appears to preserve volumes at the expense of concentrations (31, 36). One could object here that such a departure from the normal reaction pattern might merely be the result of a fall in plasma volume and the consequent circulatory depression. However, the finding of Moss (34) that miners dehydrated by sweating are more susceptible to water intoxication than normal individuals, does suggest that the original statement has some basis in fact.

Of the importance of renal control of acid-base balance as it bears on our discussion, we can say only a little without becoming involved in a problem complex in its own right. It should be noted, however, that the ability of the kidney to maintain acid-base balance is to a considerable extent dependent upon an adequate urine volume; and in dehydration from any cause, the ease with which acidosis or alkalosis can be produced is greatly exaggerated. On the other hand, acidosis, by presenting amounts of anion to the kidney in excess of its capacity for base conservation, is likely to lead to a loss of body base and, as a corollary, to a secondary loss of body water.

The role of the kidney in excreting metabolic wastes also requires some comment. In dehydration, of course, urine volume is small, but, even in complete water deprivation, some urine continues to be excreted. Although primary base depletion favours, as we have seen, the excretion of extra body water, the output in this condition is mainly, as in water deprivation, a function of the water intake. According to Lashmet and Newburgh (28), the urine in dehydration is likely to attain a specific gravity greater than 1.030 if renal concentrating power is normal, and contains 6 to 8% solids. Since the solids presenting for excretion total 40 - 60 g. per day in the human adult, it is evident that a urine volume of something over 500 ml. is necessary if the kidney is to fulfill its excretory function. This is roughly the level to which the output falls in human subjects exposed to water deprivation (6, 30, 35), but 24-hour outputs much below this may be encountered (6). Since, below the so-called "augmentation limit" of urine formation (which is about 2 ml. per min. in man) the rate of urea excretion falls with the square root of the urine volume (3), the azotaemia of severe dehydration is readily understandable. Conversely, Winkler *et al.* have demonstrated a positive correlation in dehydrated human subjects between urine volume and urine nitrogen (45), so that not only does the low urine volume in this state interfere seriously with the excretion of nitrogenous wastes, but also, the necessity to excrete these metabolites appears to be one of the chief factors limiting the kidney's ability to conserve water. Thus it has been shown in both dogs (7) and in man (44) that starvation or high protein diet aggravates dehydration, while the intake of carbohydrate, because of its protein-sparing action, tends to slow the loss of body water.

Conclusion

In conclusion, I should like to recapitulate the more fundamental principles underlying our discussion. We began by emphasizing the division of body fluids into more or less distinct phases or compartments; and because of their partial independence, an independence based essentially on a differential distribution of protein and electrolyte, we noted that dehydration may be limited to the extracellular compartment, with or without a reduction of total body water. Secondly, throughout our discussion, we have had to refer repeatedly to the close relationship between body water and its contained solutes. We have seen that primary electrolyte loss leads to a form of dehydration all the more serious because it cannot be corrected by water alone. And we found that adjustments between extracellular and intracellular compartments, renal control of body water, and thirst—indeed, virtually all of the homeostatic mechanisms which enable the organism to preserve this aspect of its internal environment—respond primarily to osmotic changes, implying, of course, a very close relation between water and solutes. In view of the ubiquity of disturbances of the body fluids in clinical medicine, it is felt that these principles can scarcely be overemphasized in the evaluation and therapy of human disease.

BIBLIOGRAPHY

(1) Austin, V. T. and Steggerda, F. G. Ill. Med. J. *69*: 124, 1936.
(2) Bernard, C. Physiologie experimentale, Vol. 2, Paris, 1856.
(3) Best, C. H. and Taylor, N. B. Physiological Basis of Medical Practice, 3d Ed., Williams & Wilkins, 1943.
(4) Black, D. A. K., McCance, R. A. and Young, W. F. J. Physiol. *102*: 406, 1944.
(5) Brull, L. and Eicholtz, F. Proc. Roy. Soc. Lond. *99B*: 57, 1925.
(6) Coller, F. A. and Maddock, W. G. Ann. Surg. *102*: 947, 1935.
(7) Danowsky, T. S., Elkinton, J. R. and Winkler, A. W. J. Clin. Invest. *23*: 816, 1944.
(8) Darrow, D. C. New Eng. J. Med. *233*: 91, 1945.
(9) Darrow, D. C. and Yannet, H. J. Clin. Invest. *14*: 266, 1935.
(10) Darrow, D. C. and Yannet, H. J. Clin. Invest. *15*: 419, 1936.
(11) Dill, D. B. Light, Heat and Altitude, Harvard University Press, 1938.
(12) Elkinton, J. R. and Taffel, M. J. Clin. Invest. *21*: 787, 1942.
(13) Elkinton, J. R. and Winkler, A. W. J. Clin. Invest. *23*: 93, 1944.
(14) Elkinton, J. R., Winkler, A. W., Hopper, J. and Hoff, H. E. J. Clin. Invest. *23*: 103, 1944.
(15) Freyberg, R. H. and Grant, R. L. J. Clin. Invest. *16*: 729, 1937.
(16) Gamble, J. L. Bull. Johns Hopkins Hosp. *60-61*: 151 & 174, 1937.
(17) Gamble, J. L., Blackfan, K. D. and Hamilton, B. J. Clin. Invest. *1*: 359, 1924.
(18) Gamble, J. L. and Ross, G. S. J. Clin. Invest. *1*: 403, 1924.
(19) Gamble, J. L., Ross, G. S., and Tisdall, F. F. J. Biol. Chem. *57*: 633, 1923.
(20) Gilman, A. Am. J. Physiol. *108*: 662, 1934.
(21) Gilman, A. Am. J. Physiol. *120*: 323, 1937.
(22) Gregersen, M. I. and Cannon, W. B. Am. J. Physiol. *102*: 336, 1937.
(23) Gregersen, M. I. and Stewart, J. D. Am. J. Physiol. *125*: 142, 1939.
(24) Hartwell, J. A. and Hoguet, J. P. J.A.M.A. *59*: 82, 1912.
(25) Hopper, J., Elkinton, J. R. and Winkler, A. W. J. Clin. Invest. *23*: 111, 1944.
(26) Hudoffsky, B., malorny, G. and Netter, H. Arch. f. die ges. Physio. *243*- 388, 1939-40.
(27) Kerpel-Fronius, E. Ztschr. f. Kinderh. *57*: 489, 1935.

(28) Lashmet, F. H. and Newburgh, L. H. J. Clin. Invest. *11*: 1003, 1932.
(29) Manery, J. F. Unpublished data.
(30) McCance, R. A. and Young, W. F. J. Physiol. *102*: 415, 1944.
(31) Mellors, R. C., Muntwyler, E. and Mautz, F. R. J. Biol. Chem. *144*: 773, 1944.
(32) Mellors, R. C., Muntwyler, E., Mautz, F. R. and Abbot, W. E. J. Biol. Chem. *144*: 785, 1944.
(33) Montgomery, M. F. Am. J. Physiol. *96*: 221, 1931.
(34) Moss, K. N. Proc. Roy. Soc. Lond. *95B*: 181, 1923-24.
(35) Nadal, J. W., Pedersen, S. and Maddock, W. G. J. Clin. Invest. *20*: 691, 1941.
(36) Peters, J. P. Body Water, Charles C. Thomas, 1935.
(37) Peters, J. P. Physiol. Rev. *24*: 491, 1944.
(38) Richter, C. P. Harvey Lect. 1942.
(39) Schechter, A. J., Cary, M. K., Carpentieri, A. L. and Darrow, D. C. Am. J. Dis. Child. *46*: 1015, 1933.
(40) Priestley, J. G. J. Physiol. *50*: 304, 1915-16.
(41) Strauss, H. Klin. Woch. *1*: 1302, 1922.
(42) Sweet, C. J.A.M.A. *107*: 765, 1936.
(43) Truax, F. Am. J. Physiol. *126*: 402, 1939.
(44) Winkler, A. W., Hoff, H. E. and Smith, P. K. Am. J. Physiol. *124*: 478, 1938.
(45) Winkler, A. W., Elkinton, J. R., Danowski, T. S. and Peters, J. P. J. Clin. Invest. *23*: 807, 1944.
(46) Wu H. and Yang, E-F. Proc. Soc. Exper. Biol. & Med. *29*: 248, 1931-32.
(47) Yannet, H. Am. J. Physiol. *128*: 683, 1940.
(48) Yannet, H. and Darrow, D. C. J. Biol. Chem. *134*: 721, 1940.

RECENT RESEARCH ON THE CHOLINESTERASES

NORMAN C. KERBEL, B.A.

Introduction

In 1914 Sir Henry Dale noted in his experiments on the effect of acetylcholine (ACh) on the heart that there was a rapid destruction of the (ACh). This was the first indication that there was an enzyme which could hydrolyze the physiologically active ester into its relatively inert constituents, choline and acetic acid. Seven years later, Otto Loewi, a pioneer in the neuro-humoral theory, published the finding that cardiac inhibition resulting from vagus stimulation was due to the liberation of a substance he called 'Vagusstoff' which was later found to be identical with ACh.

Loewi later discovered that aqueous extracts of heart destroyed the 'Vagusstoff'. This destructive agent was thermolabile and possessed other characteristics of an enzyme; hence it was considered an ACh esterase. In succeeding years, the enzyme-like nature of this destructive agent was established and finally in 1932 Stedman *et al* (1) differentiated this enzyme from other enzymes and proposed for it the name cholinesterase (ChE).

Differentiation of the Enzymes

Until quite recently, it was not known whether the ChE of blood was specific for only esters of choline, or whether it would hydrolyze other esters such as tributyrin or methylbutyrate. Furthermore, it was not known whether the ChE was only one enzyme or two or more enzymes. These problems have now been cleared up, largely due to the research of Dr. Bruno Mendel and his associates who work in the Banting and Best Department of Medical Research of this university.

Dr. Mendel and his group performed a series of experiments (2) in which the following points were clearly established—

(*a*) There is present in the animal body at least two enzymes capable of hydrolysing ACh.

(*b*) One of these enzymes, named pseudo ChE could hydrolyze esters other than the esters of choline; that is Mendel and Rudney (3), found this enzyme to be non-specific.

(*c*) The other enzyme named true ChE (3), was found to be specific for esters of choline.

In order to determine the nature and proportion of the enzymes present in any organ or tissue, a method was devised which allowed for the differentiation between the true and pseudo ChE (4). The method was based on the fact that true ChE (and not the pseudo) will hydrolyze acetyl-B-methylcholine whereas the pseudo ChE (but not the true) will hydrolyze benzoylcholine. With this method of assay as a tool Mendel *et al* discovered that the pseudo ChE was present in the blood sera of most mammals and in various other sites such as the pancreas of the dog. However, the localization of the true ChE was more definite; it was found exclusively and without exception in the erythrocytes,

muscle, and white and grey matter of the nervous systems of all animals tested. A staggering amount of work has been done recently on the localization of the enzyme. There is summarized below some of the findings of various groups of workers.

Site	*True ChE*	*Pseudo ChE*
erythrocytes	" "	
serum	" "	" "
pancreas	" "	" "
nerve tissue	" "	
muscle	" "	
ovary		" "
thymus	" "	" "
parotid	" "	" "

It should be borne in mind that there can be wide variations in the distribution of the enzymes. For example, although there may be a mixture of both enzymes in the sera of most mammals, in ruminants (ox and sheep) the true ChE alone appears in the sera. Furthermore, either the true or the pseudo or a mixture of both enzymes have been found in the pancreas and parotid gland of various species.

Significance of the Pseudo ChE

There is now much evidence available leading to the conclusion that the pseudo ChE is unimportant physiologically. Using a drug (Hoffman La Roche Nu 683) which has the ability to inhibit the pseudo ChE at concentrations at which it hardly affects the true ChE, Hawkins and Gunter (5), working in Dr. Mendel's laboratory, found that no ill effects resulted even when the serum pseudo ChE was reduced by 90%. In these in vivo experiments, the true ChE of the serum and erythrocytes was not significantly inhibited. In other experiments in which the true ChE was inhibited to the extent of 47%, symptoms of 'ACh poisoning', such as excessive salivation, defaecation, yawning, etc., were evident.

Hawkins and Gunter sum up their experiments by stating that ". . . it is evident that symptoms characteristic of ACh poisoning fail to appear when an almost complete inhibition of the activity of the specific ChE has been brought about and that these symptoms are not elicited unless a concomittant inhibition of the activity of the specific ChE has been effected." They therefore conclude that the pseudo ChE does not play an important part in the hydrolysis of ACh in vivo.

The significance of the pseudo ChE can also be questioned on the grounds that it is entirely absent from the tissue of the ruminants that were tested. In view of this and much other evidence, it becomes impossible to regard as important the tremendous amount of work done in the years between 1930 and 1943 (and indeed which is still being carried on) which is based solely on the relationship between the level of serum ChE and various diseases and dietary deficiencies. We

have seen that the amount of ChE in the blood is usually a function of two factors, the amount of true ChE and the amount of serum ChE and since the latter of these is extremely variable and since, to say the least, its physiological importance is unknown, then it is obvious that we cannot draw valid conclusions from work dependent on the sum total of these two factors.

Significance of the True ChE

The most important aspect of studies on the true ChE has been in connection with the theory of the chemical mediation of nerve impulses. Very briefly, this theory as developed by Dale, Loewi, Brown, Feldberg and others (6) states that ACh is liberated at the nerve ending and that having crossed from the post ganglionic endings to a muscle or gland, from the preganglionic endings at the synapse, or from the motor nerve at the end plates, it proceeds to act directly on the effector cell or second neuron. ChE is pictured as acting to remove the ACh with "flash-like" suddenness.

Recently, however, a new theory for the neurohumoral mechanism which differs from the theory as presented by Dale has been put forward by David Nachmansohn in numerous recent reviews and articles (7, 8, 9) Nachmansohn's hypothesis is based mainly on evidence acquired from experimental work done with the enzyme system concerned in the removal of ACh. Nachmansohn points out that the enzyme system specifically responsible for the hydrolysis of ACh is found mainly in the nerve cell and feels that a study of this enzyme will give more precise and accurate information than the study of ACh itself. He says that "all nerves contain the same specific enzyme, whether they belong to invertebrates or vertebrates, to mammals or fish. All contain a high concentration of ChE, whether sympathetic or parasympathetic, autonomic or central nervous system, efferent or afferent; the order of magnitude is always the same and sufficient to permit the assumption that the substrate, ACh, is metabolized at a rate parallel to that of the electric changes, that is the passage of the impulse".

Nachmansohn pictures the role of ACh not as an extracellular process but as an intracellular process where the rapid appearance and removal of ACh acts to increase the permeability of the polarized membrane surrounding the nerve. The polarized state of the membrane is due to a selective permeability of K ions which are more concentrated inside the axon than outside. During the passage of the impulse, the permeability of the membrane to all ions is increased and a depolarization occurs. The depolarized point becomes negative to the adjacent region and a flow of current results which stimulates the next following point. There again ACh is released and the whole process is repeated. The impulse is thus propagated along the axon. At the nerve ending, no release of ACh takes place and in this detail the concept of Nachmansohn differs most widely from that of Dale; whereas the old theory accounts for synaptic transmission by picturing a flow of ACh across the gap, the new one says that it is an electric current that bridges the synapse.

The new theory has been supported by a wealth of experimental work.

However criticism of the theory has lately increased (10, 11) and it should not be supposed that the hypothesis goes unchallenged. In an article of this nature it would be impossible to discuss the details of the arguments put forward on either side.

Conclusion

It is obvious that the above paragraphs do not attempt to cover all the aspects of the subject under discussion; furthermore, the few topics that were chosen were treated in the briefest manner possible. It is not generally realized how popular the problem of ChE has become. To quote Mann and Lutwak Mann (12), "The abundance of ChE in animal tissues and the ease with which its activity can be assayed, added to the general physiological interest of the problem, always assure a steady flow of research dealing with various aspects of the enzyme".

This article is a greatly condensed summary of a thesis presented before the Toronto Physiological Seminar Club on January 22, 1947 and I would like to thank again Dr. Mendel, Dr. Hawkins and Mr. Rudney for the help they have so graciously given me.

REFERENCES

(1) Stedman, E., *et al*, Biochem. J., *26:* 2056, 1932
(2) Mendel, B., and Rudney, H., Science, *100:* 499, 1944
(3) Mendel, B., and Rudney, H., Biochem. J., *37:* 59, 1943
(4) Mendel, B., *et al*, Biochem. J., *37:* 473, 1943
(5) Hawkins, R., and Gunter, J., Biochem. J., *40:* 192, 1946
(6) Dale, H. H., Harvey Lectures, *32:* 229, 1936-37
(7) Nachmansohn, D., Vitamins and Hormones, *3:* 337, 1945
(8) Nachmansohn, D., Currents in Biochemical Research, p. 335, 1946
(9) Nachmansohn, D., *et al*, J. Neurophysiology, *10:* 11, 1947
(10) Feldberg, W., Physiol. Revs., *25:* 596, 1945
(11) Gilman, A., *et al*, J. Neurophysiology, *9:* 245, 1946
(12) Mann and Lutwak Mann, Ann. Rev. Biochem., *14:* 250, 1944

CANCER OF THE BODY OF THE UTERUS

C. L. ASZKANAZY, M.D.

INTRODUCTION
INCIDENCE
ETIOLOGY
PATHOLOGY—adenocarcinoma
pathological classification
gross appearance
microscopic picture
adenocanthoms
spread
clinical classification
SYMPTOMS AND SIGNS
DIAGNOSIS—differential diagnosis
methods of diagnosis
SUMMARY

Introduction

Cancer of the body of the uterus is not a rare disease. It is the second most common malignancy of the female genital tract, being exceeded in frequency only by carcinoma of the cervix. In 14 series of cases of malignant disease of the uterus, the percentage incidence of fundal carcinoma varied from 2% (Knauer) to 30% (Mahle). It is commonly assumed that the ratio of cancer of the corpus to that of the cervix is 1:8. Hurdon (III) states that there is a definite increase of endometrial cancer, both absolutely and in relation to carcinoma of the cervix. Two factors are probably, at least in part, responsible for this increase: A large number of cases are recognized since better diagnostic methods are available now and patients report to the doctor more frequently; and due to the successful fight against infectious diseases, more women reach the age at which the incidence of endometrial cancer reaches its peak.

Incidence

The age incidence of the disease in five groups of cases varied from 21 to 78 years. The vast majority occurred in the 50 to 69 year age group. The average age is variously given as 54 (II), 55 (18) and 58 years (5. 28).

TABLE I

AGE INCIDENCE OF CARCINOMA CORPORIS UTERI

Graves (II)	33 - 72 yrs.	Scheffey and Thudium (24)	37 - 69 yrs.
Barns (3)	31 - 74 yrs.	Watkins and Neilson (29)	39 - 78 yrs.
Mahle (18)	21 - 73 yrs.		

Thus most of the women are past the menopause. Of the patients of Cosbie and Henderson (5), 80% were post-menopausal, of Scheffy and Thudium (24) 76.4%, and of Norris and Dunn 69.5%.

The majority of patients have borne children. In eight groups of patients the incidence of nulliparous women varied from 24.6% to 51.6% with an average of 35.2%. Since only 20% of women in the total population do not bear children,

TABLE II

Percentage Incidence of Nulliparous Patients

Graves (II)	36.6%	Healey and Cutler (12)	25.0%
Hurdon (III)	47.4%	Mahle (18)	33.0%
Claypons (III)	24.6%	Scheffey and Thudium (24)	36.7%
Barns (3)	51.6%	Watkins and Neilson (29)	26.9%

there is relatively a preponderance of nulliparous women among patients with carcinoma of the corpus uteri. Hurdon (III) reports that this type of cancer experiences a great rise among nulliparae in England.

Etiology

The etiology of cancer of the body of the uterus is unknown, but several theories have been advanced.

Although one would expect the presence of some hereditary factor predisposing to malignant growth, Watkins and Neilson (29) found only a 31% incidence of carcinoma in the families of their patients.

Graves (II) believes that impaired drainage due to partial obstruction, such as stenosis of the internal or external os, scars of the vagina or perineum, or a rigid hymen, is an important etiological factor.

Irritation, especially due to submucous fibroids, has often been mentioned as a possible cause. It is well known that fibroids frequently coexist with carcinoma of the endometrium. Scheffey and Thudium (24) report an incidence of 23.5%, Graves (II) of 25.7%. Since this is in excess of the incidence of fibroids in the general population, this is a factor which must be borne in mind. However, the presence of fibroids may only indicate a state of hormonal imbalance, which leads us to the next theory.

The location of endometrial carcinoma in the genital tract led quite naturally to the assumption that it is caused by oestrogenic stimulation. Several facts are mentioned in support of this theory.

One of these is the coexistence of the oestrogen secreting granulosa cell and theca cell tumours of the ovary and fundal carcinoma (7, 14, 16, 20, 26). Stohr(26) reports the case of a patient suffering from endometrial carcinoma and granulosa cell tumour, in whom the uterine malignancy regressed after removal of the ovarian growth. Yet Dockerty (7) found only 1 cancer of the corpus uteri among 10 cases of theca cell tumour, and only 3 among 32 patients with granulosa cell tumours. The presence of these tumours may be purely accidental, just like that of other cancers. Scheffey and Thudium (24), e.g., had among their cases of fundal carcinoma 5 patients with other malignancies, 3 of the breast, 1 of the stomach, and 1 of the bowel; Maliphant (19) even reports a case of coexisting adenocarcinoma of the corpus uteri and epidermoid carcinoma of the cervix.

It has been stated as further proof for the oestrogenic theory, that a hyperplastic endometrium is present in the great majority of patients with fundal carcinoma. Taylor and Miller (27) found hyperplastic endometria in 15 out of their 34 cases. Herrell (13), who studied the ovaries and endometria of 50 patients with carcinoma of the corpus uteri, came to similar conclusions, which are summarized in Table III.

TABLE III

Endometrium and Ovaries in Fundal Carcinoma

Endometrium	*Cases*	%	*Ovaries*	*Cases*	%
Proliferation without cystic change	14	28	Cystic	12	24
			Cystic plus carcinoma	1	2
			Not Cystic	1	2
Proliferation with cystic change	34	68	Cystic	23	46
			Cystic plus carcinoma	7	14
			Not cystic	4	8
Differentiative	2	4	Cystic	2	4
			Cystic plus carcinoma	0	0
			Not cystic	0	0

Geist and his co-workers (9) report a borderline case between endometrial hyperplasia and carcinoma. That an active endometrium is necessary for fundal cancer to develop is also indicated by the absence of such tumours in castrated females. Further, Randall (21) claims that a late menopause, which indicates an active endometrium, is a predisposing factor for cancer of the body of the uterus; and 35% of his patients had the climacteric after 51 years of age.

Other workers, however, could find no evidence of endometrial hyperplasia being a predisposing factor for malignant growth. Jones and Brewer (15), who examined 49 postmenopausal carcinomatous uteri, report that the majority contained atrophic endometrium. Fahlund and Broders (8), reviewing 236 postmenopausal specimens at the Mayo Clinic, found hyperplasia in 80% of nonmalignant, and only in 58% of cancerous endometria. The mistake of previous workers obviously was due to their failure to examine a control group of nonmalignant uteri.

An exceedingly small group of carcinomata develop from malignant degeneration of a benign polyp.

Summarizing, one may say that further work must be done on all the above theories, before any definite conclusions can be drawn.

Pathology

Two types of c rcinom occur in the endometrium, the adenocarcinoma and he adenocanthoma.

Adenocarcinoma:

The adenocarcinoma constitutes the great majority of cancers of the body of the uterus and will be discussed first.

Pathological classification:

Some workers, like Scheffey *et al.* (25) and Hurdon (III), divide these tumours into (1) highly differentiated, (2) intermediate, and (3) undifferentiated types. The majority of pathologists use Ewing's classification, which has four groups:

(I) superficial papillary adenoma malignum
(II) adenoma malignum
(III) adenocarcinoma
(IV) diffuse anaplastic carcinoma

The incidence of various types is given in Table IV.

TABLE IV

Incidence of Types of Adenocarcinoma

Groups	*Mahle (18)*	*Healey and Cutler (12)*	*Watkins (29)*
I & II	66.7%	44.9%	44.4%
III	29.0%	42.0%	37.2%
IV	4.3%	13.1%	18.6%

Gross Appearance:

The tumour arises from a single focus in the glands of the endometrium. A number of cases remain localized, but the majority spreads superficially along the endometrium until often the whole uterine cavity is involved.

The common type of growth is a broad based polypoid or fungoid mass; only rarely a thin stalk is found. There is extensive surface ulceration and, in the later stages, necrosis. The tumour is very friable and this, together with the ulceration, results in a sanguinous discharge. In a localized growth, the size, shape and mobility of the uterus remain unaltered.

The infiltrating type, which is uncommon, uniformly invades the walls, producing a bulky, firm and regular uterus. The cavity is either of normal shape or distorted by irregular projections. If the tumour involves the peritoneal surface, the uterus is grossly enlarged, fixed to adjacent structures by adhesions and presents nodular excrescences beneath the serosal covering. The uterus has often a lumpy appearance due to the presence of fibroids.

Microscopic Picture:

The glands are increased in number and have irregular and bizarre convolutions. The malignant cells are polyhedral, of irregular size and contain dark staining nuclei which show frequent mitoses. Novak (IV) grades the carcinomata according to the percentage of abnormal epithelial cells present: Grade I has 25% of less malignant cells, Grade II—25-50%, Grade III—50-75%, and Grade IV—75-100%. In Grade IV carcinoma, the cells are stratified, sometimes so extensively that the glands appear solid and resemble squamous carcinoma. There is a very atypical gland pattern and marked anaplastic changes in the cells and their nuclei.

Adenocanthoma:

A rare form of carcinoma of the corpus uteri is the adenocanthoma, which consists of a mixture of glandular and squamous epithelium. Ayre (1), Beecham and Friday (4), Cosbie and Henderson (6), and Schattenberg and Zisking (22) have recently reported cases. The incidence of this tumour is very low. Adenocanthomata constituted 0.8% of Scheffey's (24) and 2% of Watkins' (29) cases of fundal carcinoma. In the Dunlap Cancer Institute, Cosbie and Henderson (6) had 6 cases from 1929-1937.

Various theories have been proposed for the origin of the squamous elements in this peculiar type of cancer. Novak (IV) suggests that the epidermoid cells arise from "indifferent cells in the mucosa. Ayre (1) suggests that they arise by metaplasia, perhaps caused by irritation; this theory is supported by the findings in a case of Cosbie and Henderson (6), where the primary tumour was an adenocarcinoma and one of the secondary nodules in the bowel an adenocanthoma.

The gross appearance is indistinguishable from an adenocarcinoma. The microscopic picture shows solid islands of squamous cells lying close to the glandular elements or even pushing their way through the columnar cells into the lumen of the glands.

There is no unanimity as to the degree of malignancy of this tumour, e.g., Novak (V) claims that the growth is very benign and metastasizes very late, whereas Meigs states that exactly the opposite is true, i.e. that the tumour is quite malignant and metastasizes early and rapidly.

Spread

Extension of fundal cancer is largely local; distant metastases occur usually only in the late stages of the disease. Locally, the tumour spreads both by direct extension and via the lymphatics. By the latter route the peritoneum, broad ligament, bowel, bladder and other adjacent structures are reached. Early secundary nodules in the vagina, especially suburethral, are not uncommon and may be the first sign of the disease.

The lumbar lymph nodes are the ones most commonly involved. From a low site, also the upper hypogastric glands, and from the cornua, along the round ligaments, the inguinal glands may be reached.

Secundaries in the ovaries occur infrequently. Lych and Dockerty (17) had an incidence of 4%, Barns (2) 7.4% and Novak (V) 4.8%. The route of the cancer cells to the ovaries is not known, but four theories have been proposed: (1) Spread via lymphatic channels, which is the view held by most workers. (2) Blood spread, which is uncommon in carcinomata. (3) Transplantation or direct extension following penetration of the tumour through the uterine wall to the peritoneal cavity; this is the probable route when carcinomatosis is present and both ovaries are involved. (4) Transtubal implantation, which is a very intriguing theory, but not tenable; for although one can imagine that clumps of cancer cells travel against the current in the Fallopian tubes like spermatozoa, it is difficult to explain the frequent occurrence of metastases in the ovaries without involvement of the tubes.

Distant metastases, by the blood stream, occur late in the disease. Every organ in the body may be involved; secundaries are found most frequently in lungs, liver and bones. Carcinomatosis by seed implantation occurs when the tumour mass extends to the peritoneum.

Clinical Classification

The American College of Surgeons has worked out the following classification of endometrial carcinomata, which is generally used in the United States:

(1) Primary case
(2) Recurrence in vaginal wall after panhysterectomy
(3) Local recurrence after panhysterectomy
(4) Remote recurrence after panhysterectomy
(5) Recurrence after supravaginal hysterecetomy
(6) Recurrence after irradiation therapy.

Each of the above groups is subdivided into:

(A) Disease limited to uterine cavity
(B) Disease involving broad ligaments
(C) Vaginal metastasis
(D) Remote metastasis.

For example, a primary case, still limited to the uterus, is designated as 1A. According to Scheffey and Thudium (25), about three-quarters of all the cases are in this group when first diagnosed.

Healey and Cutler (12) use a different classification, which is based entirely on clinical signs:

Group I —uterus normal in size, with a depth of 3 inches.
Group II —moderately enlarge uterus, up to $2\frac{1}{2}$ months pregnancy, with a depth up to 4 inches.
Group III—grossly enlarged uterus, with a depth of 5 inches or more.
Group IV—extension of the disease beyond the uterus.

Symptoms and Signs

The chief symptom of endometrial carcinoma, which according to Watkins and Neilson (29) is found in 88.4% of all cases, is a sanguinous discharge from the vagina. In women who are still menstruating, this may take the form of menorrhagia or metrorrhagia. Women past the climacteric usually have spotting which gradually increases to a continuous flow of blood. According to Scheffey *et al.* (25), 27% of patients suffer at first from a watery or mucous malodorous discharge. In a few cases, this remains the only symptom. Pain, which was present in 33% of the women in one of Scheffey's (23) groups, is always a late symptom, which indicates extension of the disease and pressure due to metastases, or is caused by complications such as pyometria.

The chief sign of the disease is the presence of the discharge, in which particles of necrotic tissue may be found on gross examination. If the disease is extensive, the uterus is enlarged and fixed and sometimes secundary deposits may be pal-

pable in the liver, vagina, or lymph nodes of the neck. Loss of weight and emaciation occur only in very late stages. Anaemia is uncommon, in spite of continuous blood loss.

Symptoms, signs, and the age of the patient will lead the physician to suspect carcinoma of the body of the uterus, but a thorough curettage is necessary to clinch the diagnosis.

Diagnosis

Differential Diagnosis:

Since the chief sign of endometrial carcinoma is bleeding, it must be differentiated from the following conditions (IV, 23):

(1) Functional bleeding and hyperplasia of the endometrium.
(2) Complications of pregnancy, such as threatened abortion, retention of products of gestation, subinvolution of the uterus, etc.
(3) Inflammatory diseases of the uterus and adnexa—
    cervical erosion
    chronic metritis and endometritis
    adnexitis
    tuberculosis of the genital tract
    senile vaginitis.
(4) Benign tumours—polyp, submucous fibroid, hydatidiform mole.
(5) Malignant tumours—
    carcinoma of cervix
    carcinoma of vulva, vagina or tubes
    malignancy of the ovary
    chorionepithelioma
    sarcoma of uterus.
(6) Generalized diseases, such as hypertension with uterine apoplexy or the blood dyscrasias.

The first two conditions are rarely a problem, since most of the patients suffering from endometrial carcinoma are past the child-bearing age. Similarly, inflammatory conditions, except the degenerative senile vaginitis which can be excluded by inspection, are uncommon in the later decades of life. Generalized diseases give evidence of their presence in other parts of the body. The differentiation from other tumours can usually be established only by diagnostic curettage.

Methods of Diagnosis:

Since the presence of cancer cells in endometrial scrapings is pathognomic of fundal carcinoma, a diagnostic curettage must be performed in *all* suspected or doubtful cases. This is a point which cannot be emphasized too strongly, especially as it is still often neglected by the practitioner. The operation should be done in hospital and great care must be exercised to avoid forcing malignant material into the tubes or perforating the uterine wall which is often softened by the degenerating tumour mass. The entire cavity of the uterus must be curetted, since a small local growth can easily be missed by mere perfunctory scraping. If negative, the curettage should be repeated at a later date.

Positive curettings do not resemble the characteristic strips of normal endometrium, but consist of large pieces of friable necrotic tissue. The scrapings from a hyperplastic endometrium can be distinguished from carcinoma by being firmer and smoother. The final diagnosis is made on the microscopic picture, which is usually very clear cut. Borderline cases between benign hyperplasia and malignancy occur very rarely.

A new method of diagnosis is the vaginal smear, which was developed by Papanicolaou and Traut (VI). This technique, which is used primarily for cervical cancer, is based on the fact that most of the uterine carcinomata are exfoliative and shed cells into the vagina. The patient is told not to take a bath or douche preceding the test. Fluid is then sucked from the fornices, spread on a slide, stained with a special stain and examined microscopically. An expert pathologist, trained in this work, can not only spot malignant cells, but can also distinguish them from cervical cancer cells. If there are suspicious clinical signs and the smear is negative, the procedure should be repeated. It is advisable to confirm the diagnosis by a curettage.

The test is satisfactory for adenocarcinoma and adenocanthoma, but is unreliable for early cases of adenoma malignum, since very few cells are shed. In a series of 53 cases, there were 7 failures: 2 of these were post-radiational with no surface cells surviving; 4 were cases of adenoma malignum; and 1 was an adenocarcinoma complicated by pyometria and occlusion of the cervix.

The smear technique is of value for the detection of early cases in the routine checkup of patients. The disadvantage is that it is not reliable for all types of carcinoma and that it requires an expert pathologist.

Summary

Endometrial carcinoma is a fairly uncommon disease of women in the 50 - 69 year age group. It is usually an adenocarcinoma, which makes its presence known by a sanguinous discharge from the vagina. It can be diagnosed accurately by thorough curettage of the uterus and microscopic examination of the tissue removed.

REFERENCES

BOOKS:

(I) Curtis, A. H., Textbook of Gynecology 1946
(II) Graves, W. P., Gynecology 1929
(III) Hurdon, E., Cancer of the Uterus 1942
(IV) Novak, E., Gynecological and Obstetrical Pathology 1940
(V) Novak, E., Textbook of Gynecology 1944
(VI) Papanicolaou, G. N. and Traut, H. F., Diagnosis of Uterine Cancer by the Vaginal Smear 1942.

ARTICLES:

(1) Ayre, J. E., Am. J. Obst. & Gynec., *49:* 261, 1945
(2) Barns, H. H. F., J. Obst. & Gynec. Br. Emp., *48:* 443, 1941
(3) Barns, H. Hl F., J. Obst. & Gynec. Br. Emp., *49:* 173, 1942
(4) Beecham, C. T. and Friday, R. H., Am. J. Obst. & Gynec., *44:* 512, 1942
(5) Cosbie, W. G., Can. Med. Ass. J., *55:* 237, 1946

(6) Cosbie, W. G. and Henderson, D. N., J. Obst. & Gynec. Br. Emp., *46:* 32, 1939
(7) Dockerty, M. B., Am. J. Obst. & Gynec., *39:* 434, 1940
(8) Fahlund, F. T. R. and Broders, A. C., Am. J. Obst, & Gynec., *51:* 22, 1946
(9) Geist, S. H., Walter, R. I. and Salmon, U. J., Am. J. Obst. & Gynec., *42:* 242, 1941
(10) Gellhorn, H., Am. J. Obst. & Gynec., *31:* 373, 1936
(11) Goldschmidt, A., Ztsch. F. Geburtsh. & Gynec., *113:* 306, 1936
(12) Healey, W. P. and Culter, M., Am. J. Obst. & Gynec., *19:* 457, 1930
(13) Herrell, W. E., Am. J. Obst. & Gynec., *37:* 559, 1939
(14) Ingraham, C. R., Black, C. O. C. and Rutledge, E. K., Am. J. Obst. & Gynec., *48:* 760, 1944
(15) Jones, H. O. and Brewer, J. I., Am. J. Obst. & Gynec., *42:* 207, 1941
(16) Kirshbaum, J. D., Am. J. Obst. & Gynaec., *46:* 573, 1943
(17) Lynch, R. C. and Dockerty, M. B., Surgery, Gynec. Obst., *80:* 60, 1945
(18) Mahle, A. E., Surgery, Gynec. Obst., *36:* 385, 1923
(19) Maliphant, R. G., J. Obst. & Gynec. Br. Emp., *50:* 59, 1943
(20) Porter, J. E. and Bramhall, R. C., Am. J. Obst. & Gynec., *42:* 912, 1941
(21) Randall, C. L., J. Am. Med. Ass., *127:* 20, 1945
(22) Schattenberg, H. J. and Ziskind, N., Am. J. Obst. & Gynec., *39:* 112. 1940
(23) Scheffey, L. C., S. Clin. N. Am., No. 1262-80, 1940
(24) Scheffey, L. C. and Thudium, W. J., Am. J. Obst. & Gynec., *34:* 1006, 1937
(25) Scheffey, L. C., Thudium, W. J. and Farell, D. M., Am. J. Obst. & Gynec., *46:* 786, 1943
(26) Stohr, G., Am. J. Obst. & Gynec., 43: 586, 1942
(27) Taylor, H. C. Jun. and Miller, R., Am. J. Obst. & Gynec., *36:* 22, 1938
(28) Ward, G. G., Am. J. Obst. & Gynec., 44: 303, 1942
(29) Watkins, R. E. and Neilson, D. R., West. J. Surg., *50:* 17, 1942.

Features

R. K. GRAHAM, Editor

J. B. BICKERSTETH, M.C., M.A.

WARDEN OF HART HOUSE
1921 - 1947

An Appreciation

HARDOLPH WASTENEYS

It is easy to remain unconscious of a privilege which is available for the enjoyment of all, and, indeed, medical students have shared the advantages of Hart House with students of every faculty, yet there is a sense in which students of the professional faculties, not least the medical faculty, are special beneficiaries. Hart House has contributed greatly to the solution of a difficult problem which confronts all the large modern universities. This problem is to discover how the considerable numbers of students, in highly specialized courses, and crowded curricula, with relatively little opportunity for any personal contact with members of the teaching staffs, can acquire, in their university career, the elements at least, of a liberal education. Something of a liberal education has been acquired, traditionally, in universities, not so much from individual formal courses of study as from the friendly extra-academic intercourse of students and teachers from all courses, faculties and schools. Such intercourse was, and is, possible in the older universities like Harvard or Oxford because of the larger teaching staffs and of the greater leisure afforded by less crowded time-tables. In the University of Toronto, as in all modern large universities, it is only possible if facilities are available for easy participation in informal clubs such as Hart House provides. In these clubs students in classics, medicine, moderns, engineering, English language and literature, dentistry, orientals or chemistry from all colleges and faculties, together may follow with the greatest economy of time, their inclinations for debates, art, music, camera, library, or crafts. Such opportunities are especially valuable for students in the professional faculties, and particularly for medicine, where the full timetable affords little leisure, and the exigencies of the course make small provision, for the cultivation of the art of living. Hart House was intended by its founders to perform this very service and various institutions and students unions have been provided in other universities with like intent but, so far as I have been able to discover, Hart House has been preeminently successful because, and only because it had the good fortune, 26 years ago, to secure Mr. Bickersteth as its Warden.

I have had a fairly close view of the Warden's aspirations and achievements in Hart House during those years and I have never ceased to marvel at his perennial enthusiasm, imagination, good humour, understanding of student outlook, meticulous attention to details, his extraordinary ability to bring the great and near great of the world to the house to meet its members, the warmth of his friendship and his great capacity for work. All these he unreservedly and selflessly placed at the service of our students in the House. In all those years he, I

believe, had no other interest and few other thoughts than of Hart House and how it might better serve the students in it.

If all this sounds extravagant, I cannot help it, for it is literally true. Bickersteth is a phenomenon, even an epiphenomenon and his wardenship has been unique. True, there have been many students who were not attracted and some who were even repelled by his personality and his mannerisms but very few indeed of the thousands who have been closely associated with him in Hart House activities, in all of which he participated himself with lively interest, have not appreciated the immense contribution he made to their understanding and enjoyment of music, art, books or printing, whatever interest they had chosen for the enrichment of their future lives.

If one wishes to discover what Hart House has done for Medical students in particular, one has only to look over the lists of medical students on Hart House committees through the past 28 years. I think, as I look over these lists, that Hart House owes a good deal also to meds. In one of the early years meds. had 29 men on Hart House committees and five meds. were on the Board of Stewards; indeed, there were five meds. on the Stewards in four of its 27 years and four meds. for another four years. In one year there were no less than 10 meds. on the House Committee and in that year, 1921-22, there were no less than 34 meds. on seven of its committees. Meds. have always been well represented on the Board of Stewards and the quality of these representatives, to my knowledge, has been as high as their numbers. Their names might not mean much to today's undergraduates though many of them are now distinguished members of the Faculty and of the Profession. To me, the list recalls many close friendships with medical students which I, and other members of the faculty, had the opportunity to form on Hart House committees, and nowhere else.

Many a med. has thought gratefully after graduation, and I think somewhat nostalgically, on the opportunities provided in Hart House, and happily used, to cultivate his tastes and learn the best in Music or Art and to meet intimately the leaders in those fields. Each one of those meds., whatever field he cultivated, felt grateful to the Founders of the House who provided the lovely fabric and formulated its purpose and ideals in the Founders' Prayer, but most of all he felt grateful for the opportunity of coming under the influence of the man who made those ideals a reality, who communicated to them some of his immense enthusiasm and the warmth of his friendship. Many of them have said to me that their chief and fondest memories of their university years would be of hours spent in Hart House and of Burgon Bickersteth.

It was during the farewell dinner to the warden in May that a member of the Board of Stewards, the "Feature Editor" of this journal, asked me to write my personal impressions of the now retired Warden. He asked this, I think, not because he believes that medical students have the least interest in my personal impressions or experiences, but in order that I might recall and review the benefits which the men of our faculty have enjoyed during and through the wardenship of this distinguished person.

After 26 years as Warden of Hart House he will, he tells me, use his well-earned leisure to become a student once more, at the University of London, in his favourite field of Mediaeval History.

Abstracts

E. R. YENDT, Editor

CONTRIBUTORS

J. S. LAUGHTON
E. A. MCCULLOCK
R. K. GRAHAM

PAEDIATRICS I

TETANUS. Nelles Silverthorne: Journal Paed., Vol. *30*, Nol 2, Feb., 1947.

THE author reports observations made on 70 patients with tetanus admitted to the Hospital for Sick Children, Toronto, during the years 1921 to 1946.

The disease was most commonly found in boys between the ages of 3 to 13 during the summer months. In fifteen of the seventy patients there was no history of injury.

The present treatment consists of constant nursing, fluids by mouth as long as possible, and than intravenous fluids, antitoxin intramuscularly in doses of 40,000 to 300,000 units, and the use of seconal as a sedative.

Results of treatment show an overall fatality of 47% with a drop in fatality rate of 66.6% in the years 1921-1928 to 28.5% in the years 1936-1946.

The improved results are explained by the use of tetanus antitoxin by the intramuscular rate only, continuous nursing, more careful feeding of patients and the use of seconal as a sedative.

The author does not recommend the intravenous or intrathecal use of antitoxin.

Active immunization as a means of preventing tetanus is discussed and recommended for all children.

E. R. Y.

PAEDIATRICS II

SULFADIAZINE PROPHYLAXIS IN CHILDREN AND ADOLESCENTS WITH INACTIVE RHEUMATIC FEVER. Janet S. Baldwin: Journal Paed., Vol. *30*, No. 3, March 1947.

THE authors report treatment of 51 inactive rheumatic children and adolescents with prophylactic sulphadiazine—for a total of 87 patient years. The drug was administered as a single daily dose varying from 0.25 gm. to 1 gm. depending upon the age of the child, which gave blood sulfadiazine levels averaging between 1.0 and 3.5 mgms. %.

In this group only one recurrence of active rheumatic fever was observed. In an equal number of closely matched controls observed throughout the same time period, one probable and six definite recurrences of active rheumatic fever occurred.

No instances of sulfadiazine toxicity necessitating permanent discontinuance of treatment was encountered.

E. R. Y.

MEDICINE I

MALIGNANT LYMPHOMA: CUTANEOUS SYMPTOMATOLOGY. D. E. H. Cleveland: Canad. M.A.J. Vol. *56*, No. 6, June 1947.

THIS article is concerned chiefly with the dermatological aspect of malignant lymphoma. The author believes that few writers with the exception of some dermatologists have given the cutaneous picture of these diseases the emphasis which it should have. He emphasizes the fact that in Hodgkin's disease and follicular lymphoma the chief signs and symptoms may very often and for prolonged periods be exhibited solely by the skin.

The records of the Vancouver General Hospital covering a ten-year period disclosed 213 proven cases of malignant lymphoma. In 30% of these, cutaneous signs and symptoms have been the predominating and often the first feature to attract attention. In over half the cases of Hodgkin's disease and in 17 of 21 cases of follicular lymphoma, the cutaneous lesions were predominating. However, such cases of lymphosarcoma and leukemia were rare.

In Hodgkin's disease, the non-specific lesions were invariably pruritic resulting in excoriation, eczematoid changes, and pigmentation. In these cases gross lymphadenopathy above the clavicles, gross mediastinal lymphadenopathy, splenic enlargement determinable clinically, and Pel-Ebstein fever were all rare findings.

The cutaneous lesions of follicular lymphoma were similar to those of Hodgkin's disease. There were no deaths from this disease in the 10 years series. However, it was impossible to distinguish between follicular lymphoma and Hodgkin's disease clinically.

E. R. Y.

SURGERY I

THE USE OF THE MALE SEX HORMONE IN WOMEN WITH BREAST CANCER. F. R. Adair, M.D., F.R.C.S.: Journal of Surgery, Obstetrics and Gynaecology, Vol. *84*, No. 4A, April 15, 1947.

HORMONE therapy in the treatment of cancer was firmly established when Huggins was able to produce cures in 25% of cases of prostatic cancer by the use of oestrogenic substances. This led to the exploration of other types of cancer related to sex hormones.

In a group of 5000 cases of early breast cancer reviewed by Dr. Adair, the greatest peak of incidence fell at the age of 45 years. This he believed to be a time when certain chemical changes deviating from the normal were occurring in the ovarian hormone, as the average age of menopause was $46\frac{1}{2}$ years. A lesser peak of incidence occurred at the age of 60 years, which is the time when almost no ovarian hormone is produced. In this latter group the use of oestrogens proved beneficial but they were of no value in the former group. Testosterone could, however, be used with success in both types.

For several years at the Memorial Hospital, New York, testosterone proprionate was used in 200 cases of cancer of the female breast without effect.

Dr. Adair then began using this substance on 48 of his private patients in much larger doses exceeding 25 mg. The most useful dose he believed to be 100 mg. 3 times a week for 8-10 weeks, but this was not established as an optimum. Under this therapy those cases with advanced breast cancer and particularly those with metastases to bone obtained marked clinical improvement as well as definite X-ray changes in certain cases. Only a small number with soft tissue metastases received any benefit. Apparently the relief was produced by surrounding the groups of cancer cells with a copious deposit of calcium salts and thus retarding their growth. It would seem that, in cases of widespread bony metastases, the use of testosterone proprionate is more efficatious, longer lasting, and practical than X-ray therapy. Masculinizing sequelae—deep voice, hair on the face, and an enlarged clitoris—in certain cases prove a source of annoyance.

Testosterone is not a cure for advanced breast cancer but its effects are profound and gratifying. Much more research, however, is still necessary before results and danger can be evaluated.

J. S. L.

SURGERY II

MUDULLARY NAILING OF FRACTURES OF THE LONG BONES. W. Russell MacAusland: Journal of Surgery, Gynaecology and Obstetrics. Volume 84, January, 1947.

THE immobilization of fractures of long bones by the introduction of a medullary nail was began by Kuentscher in Germany in 1940 and was used there extensively during the war.

The modified method employed by Dr. MacAusland consisted of introducing a V-shaped tantalum nail of suitable size and length into the proximal fragment distant to the site of fracture. The site of fracture was then opened, the ends of the fragments cleaned and approximated, the nail was directed into the wound and drawn into the distal fragment.

A. The advantages of medullary nailing are:—
   (1) Absolute immobilization is insured.
   (2) The adjacent joints remain free to be moved.
   (3) Ambulation is possible at an early date.
   (4) The sequelae of rigidity, circulatory disorders and atrophy from disuse are averted.

B. The fractures best treated by this method may be enumerated as follows:
   (1) Fractures of the femur above the middle third, of the transverse or short variety. This method offers a solution for the treatment of fractures of the femur below the great trochanter in which it is difficult to control medial displacement of the distal fragment as well as for comminuted fractures in this area.
   (2) Slanting and comminuted fractures of the upper end of the humerus difficult to control by other means.

(3) Fractures of both bones of the leg at the junction of lower and middle third where healing is always slow to avoid stiffness of the ankle and knee.

C. Contraindications.

(1) Fresh open fractures of the limb (although this is controversial).
(2) Infected fractures.
(3) Fractures in children.

This method of treating fractures is as yet in its infancy and still under discussion. The method does, however, have the great advantage of providing absolute immobilization at the same time leaving free the adjacent joints for use at an early date.

J. S. L.

SURGERY III

MECKEL'S DIVERTICULUM. William R. Moses: N. Eng. Jour. Med. 237, 4.

THE author briefly discusses the incidence, anatomy, pathology and clinical importance of Meckel's Diverticulum. The incidence is one in two hundred. He classifies the clinical groups as follows: (1) Peptic group, associated with ulcer symptoms, haemorrhage or perforation. (2) Obstructive group, associated with volvulus, intussception, strangulated hernia, etc. (3) Diverticular group, associated with acute or chronic inflammation of the diverticulum. (4) Umbilical group, associated with fecal fistula, or other anomoly based on development. (5) Tumor group. (6) Incidental, asymptomatic group.

The frequency with which the complications have been reported in the literature are reviewed, and the author reports two interesting cases.

E. A. M.

SURGERY IV

CANCER OF THE RECTUM. E. J. Ottenheimer: New England Journal of Medicine. Vol. *237* No. 1, pp. 1-7.

THE author discusses cancer of the rectum as it occurred in 35,000 cases of cancer collected in a co-operative effort in Connecticut in the period 1935-1945. Of these cases from 4 to 5 per cent were cancer of the rectum. In this eleven-year period 1610 cases were admitted to hospital, 1188 being proven by microscopic section and the remainder being clinical diagnoses.

In this series the age distribution of cancer of the rectum was in the group 50-59 years, 60% of the cases occurring in this group. There seemed to be only a slight hereditary tendency.

The signs and symptoms in the order of importance were: rectal bleeding, loss of weight, change in bowel habit, local pain and tenesmus. Eleven per cent gave haemorrhoids as the presenting symptom. In this series 20% had cardio-vascular derangements, 2.3% diabetes, 1% gastric ulcers. Delay in reporting symptoms fell from 11.2 months in 1935 to 6.9 months in 1937, but no further improvement has occurred.

Because of the striking symptoms indicating a lower bowel disorder, the author states that with the aid of digital, proctoscopic, X-ray, and biopsy the diagnosis should be made early.

In this group of cases, 59.5% were localized cancers, 26.6% had regional involvement of the lymph nodes, and 13.9% had distant metastases. Some 46% of the cases were resectable in 1935, but this figure rose to 62.4% in 1945.

Treatment given was: in about 50% of cases radical resection; in a considerable number local excision, which was performed in cases with malignant change in a previously benign polyp; in a very few only radiation; in 275 cases colostomy was performed with a 28% mortality rate; in 105 cases no treatment was given due to advanced age, debility, or remote metastases.

In the vast majority—74.6%—a one-stage abdomino-perineal operation was performed with a mortality of 14.7% in the year 1945. The causes of death were in order of importance: peritonitis, shock, cardio-vascular failure, pulmonary embolism, pneumonia, atelectasis, and urinary complications.

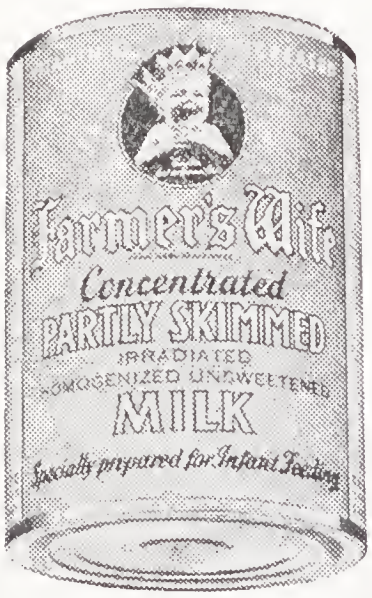
The author states that although a detailed analysis of these cases has not been presented, he has indicated the value in collecting such data. Attention should be drawn to the striking symptoms. Biopsy must be done for accurate records. Operability and mortality rates are improving. In the period 1935 to 1940 the five-year cure rate was 7.9% of all cases and 11.5% of all the microscopically proved cases.

R. K. G.

A Lower Fat Content Milk
For Infant Feeding . . . .

"FARMER'S WIFE"

PARTLY SKIMMED MILK



. . . with Vitamin D Potency of 400 International Units per reconverted quart (half "Farmer's Wife"-half water).

You can recommend this milk for artificial feeding of infants.
High in protein value and lower in fat content.

Please send for literature and pocket formula card.

COW & GATE (CANADA) LIMITED
GANANOQUE, ONTARIO

AN EXPECTORANT MIXTURE

for the Treatment of
ACUTE BRONCHITIS
CHRONIC BRONCHITIS
ASTHMATIC BRONCHITIS

Cross Section of lung showing (acute) purulent bronchitis (human)

Photograph: H. R. Hayden, F.R.P.S.

"NUSILYN"

During the exudative stage of acute respiratory infections, administration of Nusilyn tends to dilate bronchi and liquefy bronchial secretions and exudates. In this way expectoration is facilitated and the respiratory tract is cleared of obstructing secretions. Hacking and unproductive cough is avoided, patients are permitted rest and comfort, and healing is promoted.

Each Fluid Ounce Contains:

Theolamine (Aminophylline "Frosst")	5 gr.
Potassium citrate	40 gr.
Tincture of Ipecac	20 min.
Chloroform	8/10 min.
Simple syrup, flavoured	q. s.

"NUSILYN" with CODEINE

Nusilyn with Codeine (1 gr. per fluid ounce) is available for those cases in which part of the cough may be due to the pre-exudative stage.

DOSAGE

ADULTS: 1 to 2 teaspoonfuls.

CHILDREN: 1 to 2 years: ¼ teaspoonful (30 drops); 2 to 4 years: ⅓ teaspoonful (40 drops) to ½ teaspoonful (60 drops).

Well diluted with water and taken every four hours.

MODES OF ISSUE

Available in 4 fl. oz. 16 fl. oz., and ½ Imp. gal. bottles.

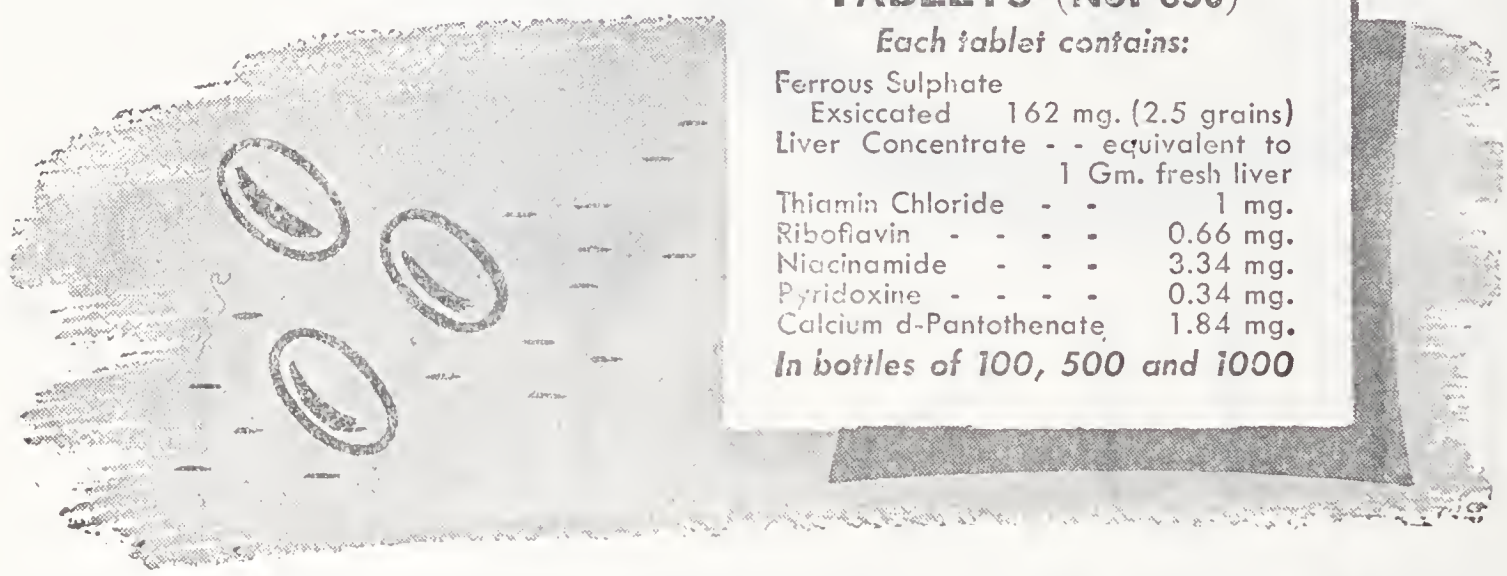
Charles E. Frosst & Co.
MONTREAL CANADA

Frosst
SINCE 1899
THE SYMBOL OF PROGRESS
IN PHARMACEUTICAL RESEARCH

IN SECONDARY ANAEMIAS

'THIRONEX'

FERROUS IRON
LIVER EXTRACT
VITAMIN B FACTORS

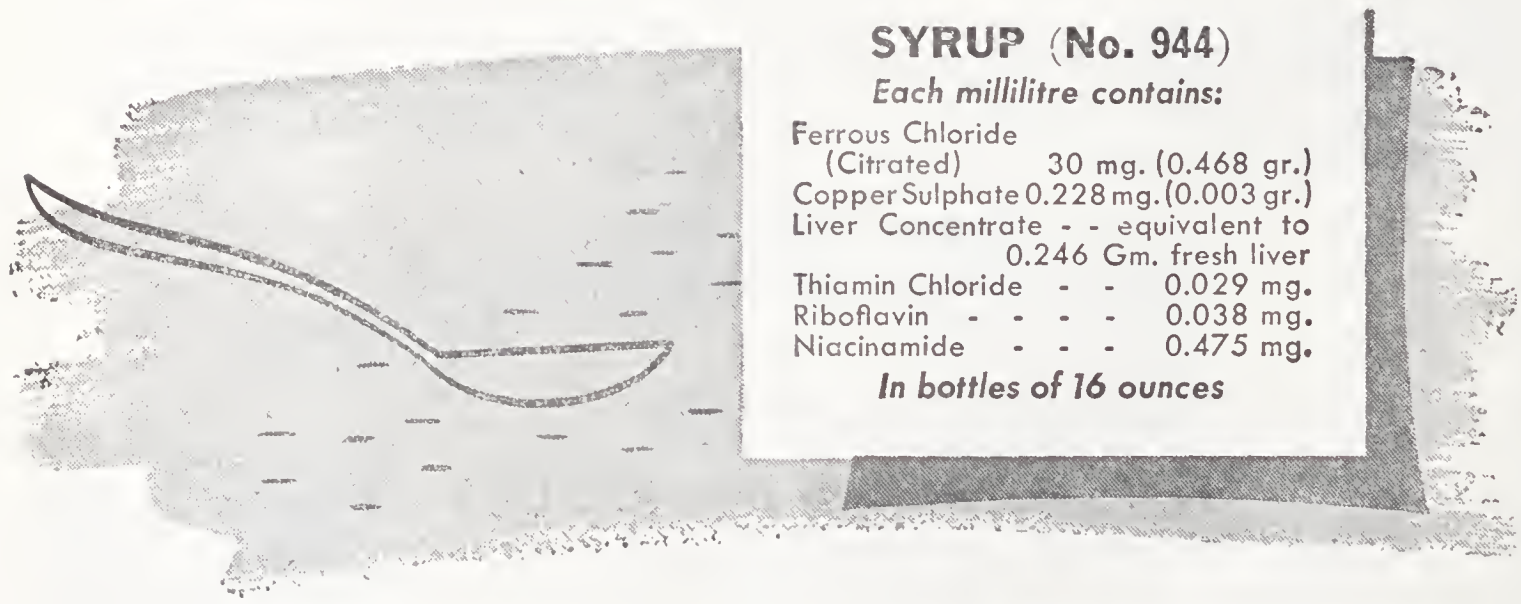


TABLETS (No. 830)

Each tablet contains:

Ferrous Sulphate Exsiccated	162 mg. (2.5 grains)
Liver Concentrate	equivalent to 1 Gm. fresh liver
Thiamin Chloride	1 mg.
Riboflavin	0.66 mg.
Niacinamide	3.34 mg.
Pyridoxine	0.34 mg.
Calcium d-Pantothenate	1.84 mg.

In bottles of 100, 500 and 1000



SYRUP (No. 944)

Each millilitre contains:

Ferrous Chloride (Citrated)	30 mg. (0.468 gr.)
Copper Sulphate	0.228 mg. (0.003 gr.)
Liver Concentrate	equivalent to 0.246 Gm. fresh liver
Thiamin Chloride	0.029 mg.
Riboflavin	0.038 mg.
Niacinamide	0.475 mg.

In bottles of 16 ounces

Ayerst

AYERST, McKENNA & HARRISON LIMITED

Biological and Pharmaceutical Chemists

MONTREAL **CANADA**